Synthesis of Novel Retinoid X Receptor-Selective Retinoids

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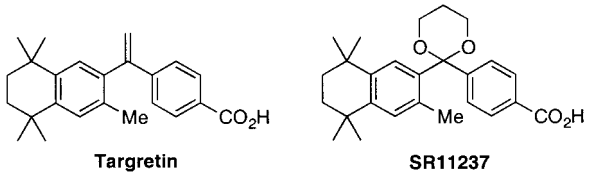
Retinoids **1**−**5** have been identified as potent RXR agonists for evaluation in the treatment of non-insulin-dependent (type II) diabetes mellitus (NIDDM). Highly convergent syntheses of **1**−**5** have been developed. The core tetrahydronaphthalene **7**, employed in the synthesis of **1** and **2**, was prepared in 98% yield using an $AlCl_3$-catalyzed (0.03 equiv) Friedel−Crafts alkylation of toluene with 2,5-dichloro-2,5-dimethylhexane **6**. A nitromethane-mediated Fridel−Crafts acylation of **7** with chloromethylnicotinate **9** was developed to prepare ketone **10** in 68% yield. Chelate-controlled addition of MeMgCl to **10** followed by dehydration afforded olefin **11** in 65% yield. Cyclopropanation of **11** with trimethylsulfoxonium ylide, followed by saponification, completed a five-step synthesis of **1** in 33% yield. $FeCl_3$-catalyzed (0.05 equiv) Friedel−Crafts acylation of **7** with chloromethyl-terephthalate **14** afforded ketone **15** in 81% yield. Saponification of **15** and reaction with 50% aqueous NH_2OH in AcOH afforded a 9:1 mixture of *cis* and *trans* oximes, from which the desired *cis*-oxime **2** was isolated in 43% yield. The core bromo-dihydronaphthalene **29** required for the synthesis of **3**−**5** was prepared by a Shapiro reaction. Transmetalation of **29** and reaction with Weinreb amides **30b** or **36** afforded ketones **32** and **37**, which were converted into **3**−**5** using chemistry comparable to the tetrahydronaphthylene series. Suzuki coupling of boronic acids **41** and **42** with vinyl triflate **43** provided an alternative approach to the synthesis of this class of compounds.

Introduction

The retinoid receptors are members of the superfamily of intracellular hormone receptors that function as regulators of gene transcription.[1−4] These receptors are classified into two subfamilies: the retinoic acid receptors (RARα, RARβ, and RARγ), and the retinoid X receptors (RXRα, RXRβ, and RXRγ).[5,6] This classification of retinoid receptors is based upon differences in amino acid structure, responsiveness toward natural and synthetic ligands, and ability to modulate gene expression of various target genes. Ligands that interact with these receptors, the retinoids, make up a structurally diverse group of molecules. Among this class of compounds, Ligand Pharmaceuticals Inc. has recently identified a new class of retinoids, Targretin and SR11237, that are selective activators of RXR and show little or no activation of RAR (Chart 1).[7] Targretin is currently under evaluation for treatment of cancer.[8−16]

Chart 1



Targretin **SR11237**

In 1997, Eli Lilly and Company and Ligand Pharmaceuticals Inc. initiated a collaborative agreement to develop a novel series of potent RXR agonists for treatment of non-insulin dependent (type II) diabetes mellitus (NIDDM). In addition to Targretin this study involved evaluation of the pyridyl cyclopropane derivative **1**[17,18] and *cis*-oxime **2** (Chart 2).[7,19] The latter compounds were

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(3) Mangelsdorf, D.; Umesono, K.; Evans, R. In *The Retinoid Receptors*, 2nd ed.; Raven Press, Ltd.: New York, 1994; pp 319−349.
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(11) Bengtson, E.; Rigas, J. *Drugs* **1999**, *58*, 57−69.
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(13) Otter, K.; Ziegler, A. *Med. Monatsschr. Pharm.* **1999**, *22*, 2−7.
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(15) Miller, V.; Benedetti, F.; Rigas, J.; Verret, A.; Pfister, D.; Straus, D.; Kris, M.; Crisp, M.; Heyman, R. *J. Clin. Oncol* **1997**, *15*, 790−795.
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(17) Allegretto, E.; Shevde, N.; Zou, A.; Howell, S.; Boehm, M.; Hollis, B.; Pike, J. *J. Biol. Chem.* **1995**, *270*, 23906−23909.
(18) Mukherjee, R.; Davies, P.; Crombie, D.; Bischoff, E.; Cesario, R.; Jow, L.; Hamann, L.; Boehm, M.; Mondon, C.; Nadzan, A.; Paterniti, J.; Heyman, R. *Nature (London)* **1997**, *386*, 407−410.

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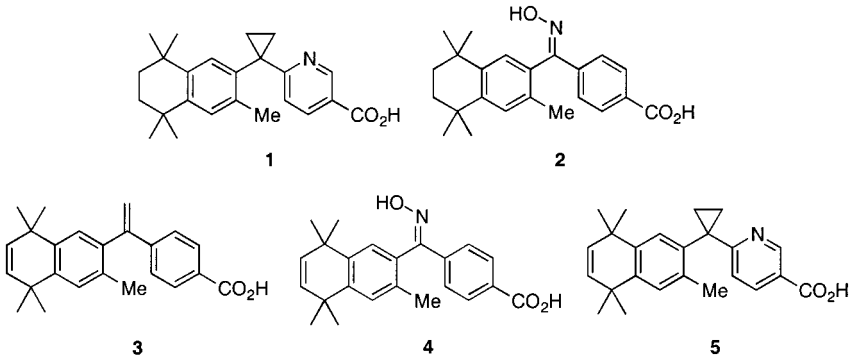
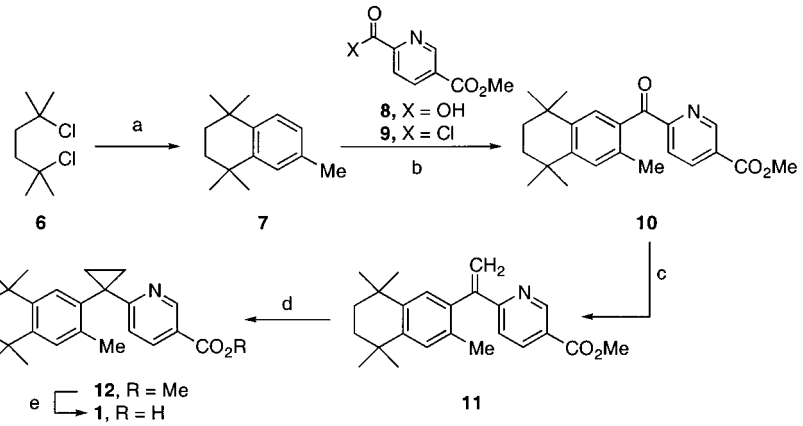
Chart 2



Scheme 1[a]



[a] Initial conditions: (a) toluene (solvent), $AlCl_3$ (3.0 equiv), 91%; (b) $AlCl_3$ (3.0 equiv), CH_2Cl_2, 50%; (c) $MePPh_3Br$, $NaNH_2$, THF, 64%; (d) Et_2Zn, $ClCH_2I$, CH_2Cl_2, 65%; (e) MeOH, KOH (aq), HCl, 80%. Developed conditions: (a) toluene (1.5 equiv), $AlCl_3$ (0.03 equiv), CH_2Cl_2, 99%; (b) CH_3NO_2 (0.5 equiv), $AlCl_3$ (2.7 equiv), CH_2Cl_2, 68%; (c) MeMgCl (1.25 equiv), THF; *p*-TsOH, toluene, 61%; (d) $(Me)_3SOI$, *tert*-KOBu, DMSO, THF, 82%; (d) NaOH, MeOH, HCl (aq), 99%.

reported to be 10 times more potent than Targretin. Concerns with metabolism of these tetrahydronaphthalene derivatives, vide infra, led to development of a second generation of dihydronaphthalene analogues **3**−**5**. A synthesis of **1** and **2** has been published in the literature,[7,19,20] although no work on the dihydronaphthalene series has been reported. Our goal was to develop a synthesis that would supply kilogram quantities of **1** and **2** and to identify a new synthetic route to prepare multigram quantities of **3**−**5** for preclinical evaluation. This manuscript is the first full disclosure of our work on this class of compounds.

Results and Discussion

Synthesis of the Tetrahydronaphthylene Derivatives 1 and 2. A synthesis of **1**, in 15% overall yield from 2,5-dichloro-2,5-dimethylhexane **6** has been reported (Scheme 1).[20] Friedel−Crafts acylation of **7** by chloromethylnicotinate **9**, prepared in 88% yield from 5-(methoxycarbonyl)pyridine-2-carboxylic acid **8**, using $AlCl_3$ (3.0 equiv) afforded ketone **10**, albeit in low yields (20−50%). Olefination of **10** with methyltriphenylphosphonium bromide/$NaNH_2$ provided olefin **11** in 64% yield. Cyclopropanation of **11** with diethylzinc and chloroiodomethane, followed by saponification afforded **1** in 52% yield. Although this route was successful, the yield of **1** was low and the intermediates required chromatographic purification. To develop a process to prepare multikilogram quantities of **1** we sought to identify alternative methods to perform the olefination and cyclopropanation reactions that would avoid generation of Ph_3PO, which is difficult to remove on large scale, and eliminate the use of pyrophoric diethylzinc and unstable chloroiodomethane. In addition, methods for crystallization of intermediates that would avoid chromatographic purification would be evaluated.

Our initial strategy was to examine the Friedel−Crafts acylation of **7** with chloromethylnicotinate **9**. However, upon examination of this reaction, vide infra, we determined that **7** was unstable to the acylation conditions and in the presence of excess $AlCl_3$ underwent competitive dimerization. This caused us to reevaluate the conditions employed for the synthesis of **7**, which involved Friedel−Crafts alkylation of 2,5-dichloro-2,5-dimethylhexane **6** in toluene using $AlCl_3$ (1.5 equiv).[21] To minimize exposure of **7** to a Lewis acid and reduce the potential for decomposition on large scale, we determined that this reaction could actually be preformed catalytically using only 0.03 equiv of $AlCl_3$ and 1.5 equiv of toluene in CH_2Cl_2 as solvent.[22] This process was extremely robust, affording **7** in reproducible yields of 99%.

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(22) Pearson, D.; Buehler, C. *Synthesis* **1972**, *10*, 533−542.

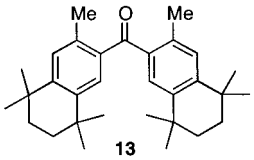


Figure 1.

A critical factor for successful formation of **10** was found to be the method employed to generate acid chloride **9**. Acid **8** is extremely hygroscopic and must be rigorously dried prior to formation of **9**. In addition only 1.0−1.1 equiv of $(COCl)_2$ should be employed for preparation of **9**, since excess $(COCl)_2$ results in formation of dimer **13** (Figure 1).[23,24] By using these conditions to generate **9** the yield of **10** was increased to 56%.

As a result of the instability of **7** to $AlCl_3$, alternative Lewis acids and solvents were evaluated to prepare **10**. Unfortunately, Lewis acids $SnCl_4$, $FeCl_3$, $TiCl_4$, and $ZnCl_2$ gave no reaction. The use of nitromethane, which is known to reduce the activity of $AlCl_3$ through reversible complexation,[25] resulted in minimal acylation of **7** after 1 h at room temperature, and decomposition occurred upon heating the reaction to 90 °C. However, when the reaction was conducted in CH_2Cl_2 containing 0.5 equiv of nitromethane (relative to **8**) the rate of acylation slowed considerably, the selectivity increased, and **10** was reproducibly isolated in 68% yield after crystallization of the reaction mixture from MeOH.

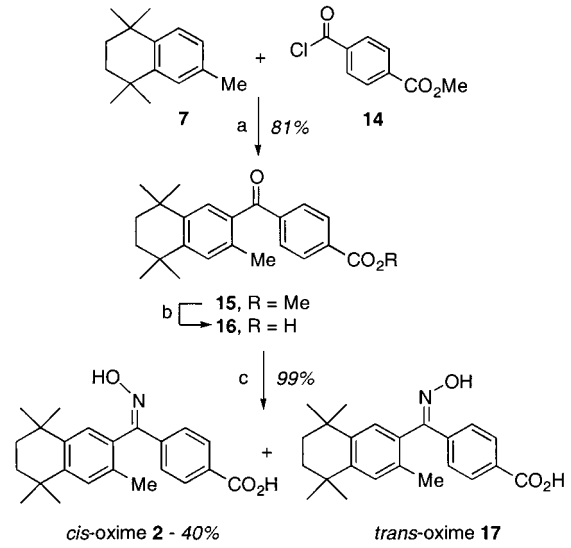
The Wittig reaction to incorporate the olefin was avoided by using a chelate-controlled addition of MeMgCl to ketone **10**. This reaction afforded only the intermediate 3° alcohol with no addition to the carboxylate ester. Dehydration of the alcohol using *p*-TsOH (1.0 equiv) afforded a 61% yield of olefin **11** after recrystallization from MeOH.

Cyclopropanation of α,β-unsaturated ketones using trimethylsulfoxonium ylide is a well-known reaction.[26] The presence of a *p*-carboxyester functionality in **11** led us to examine the use of this reagent for the synthesis of **1**. Thus, reaction of **11** with trimethylsulfoxonium ylide (2.0 equiv), generated from trimethylsulfoxonium iodide/NaH in DMSO, afforded **12** in 65% yield. However, olefin **11** was insoluble in DMSO, and the reaction proved difficult to perform on large scale. To avoid this problem the ylide was generated in THF using *tert*-KOBu as base. This approach afforded cyclopropane **12** in reproducible yields of 82% after trituration from MeOH. Saponification of **12** afforded **1** in 99% yield.

The development outlined above completed a five-step synthesis of the pyridyl derivative **1** in 33% yield. The synthesis is extremely robust, involves no chromatographic purification, and has been successfully employed to provide **1** in kilogram quantities.

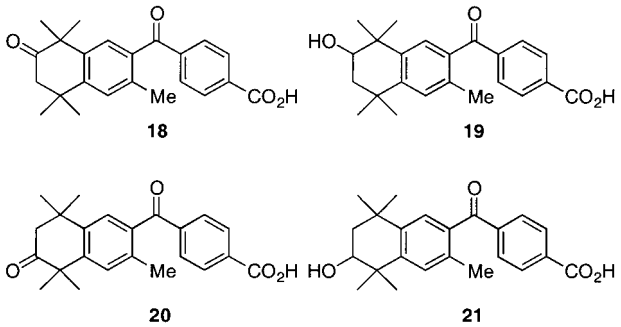
Cis-oxime **2**, a more potent RXR agonist than the corresponding *trans*-oxime **17**,[19] is prepared from ketone **15** generated by Friedel−Crafts acylation of **7** using $AlCl_3$ (2.7 equiv) with commercially available chloromethylterephthalate **14** (Scheme 2). Again, as a result of the instability of **7** to $AlCl_3$, we sought to develop a catalytic method to prepare **15**. Unfortunately, by using 0.05 equiv of $AlCl_3$ or $SnCl_4$, **15** was obtained in only 5% and 14% yield, respectively. Alternative Lewis acids such as $BF_3 \cdot Et_2O$, $ZnCl_2$, or I_2 gave no reaction. However, acylation of **7** with **14** using 0.05 equiv of $FeCl_3$ afforded **15** in 81% isolated yield. This afforded an extremely efficient process for preparation of **15**, a key intermediate for the synthesis of oxime **2** and Targretin. Saponification of **15** afforded acid **16** in quantitative yield.

Scheme 2[a]



[a] (a) $FeCl_3$, (0.05 equiv), $Cl(CH_2)_2Cl$; (b) MeOH, 50% aq. NaOH; (c) 50% aq NH_2OH, HOAc, reflux.

Chart 3



Ligand reported a synthesis of **2** from **16** in 88% yield using $NH_2OH \cdot HCl$ in pyridine/ethanol.[19] However, upon scale-up we found that reaction of **16** with NH_2OH in EtOH or DMSO/H_2O was very slow (2−3 days) even at reflux temperatures and generated a 7:3 mixture of *cis*- and *trans*-oximes. Use of excess NH_2OH in EtOH led to slightly faster reaction rates, but esterification of **16** by ethanol was observed. However, the rate of the reaction was improved by performing the reaction with aqueous NH_2OH in AcOH at pH 4. This afforded *cis*- and *trans*-oximes **2** and **17** in 99% yield and 9:1 selectivity. Crystallization of the reaction mixture from 3:1 hexanes/EtOAc afforded a 43% yield of *cis*-oxime **2**, whose structure was confirmed by comparison to the literature data (Scheme 2).[27] This work completed an efficient synthesis of **2** in three steps and 34% yield from **7**.

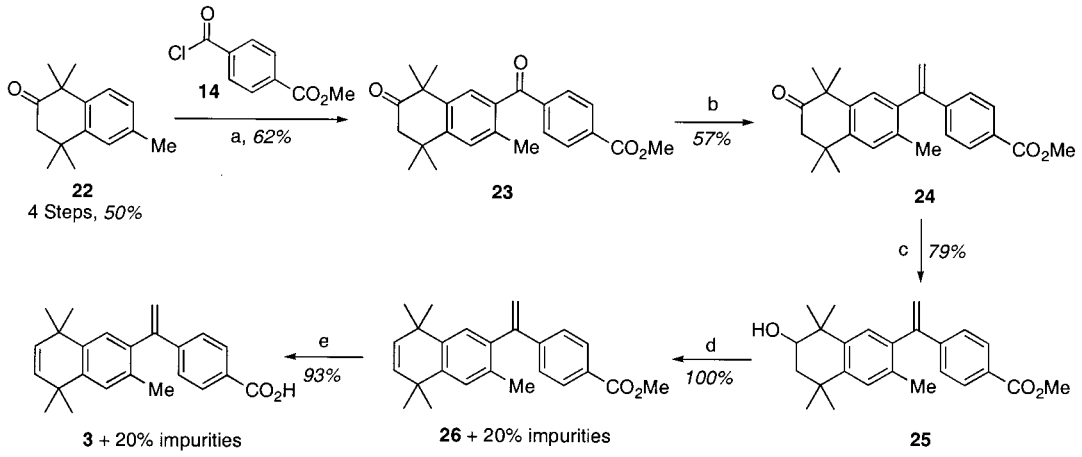
(23) Heirtzler, F.; Hopf, H.; Jones, P.; Bubenitschek, P.; Lehne, V. *J. Org. Chem.* **1993**, *58*, 2781−2784.

(24) Dimer **13** was identified by GC-MS (MW = 430). FTIR confirmed the presence of a carbonyl stretch at 1655 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 2H), 7.19 (s, 2H), 2.44 (s, 6H), 1.66 (s, 8H), 1.31 (s, 12H), 1.15 (s, 12H).

(25) Olah, G.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448−7461.

(26) Evans, D.; Tanis, S.; Hart, D. *J. Am. Chem. Soc.* **1981**, *103*, 5813−5821.

Scheme 3[a]

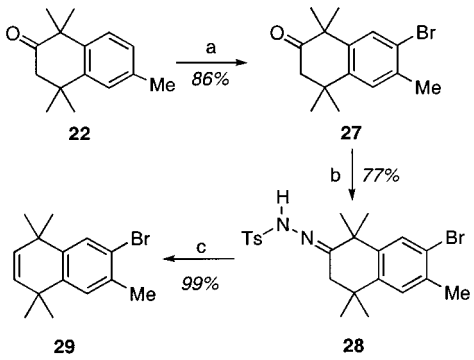


[a] (a) $AlCl_3$ (4.0 equiv), $Cl(CH_2)_2Cl$; (b) $MeP(Ph)_3Br$, $KN(SiMe)_2$, THF/toluene; (c) $NaBH_4$, MeOH; (d) $POCl_3$, pyridine, 100 °C; (e) 50% aq NaOH, MeOH, HCl (aq).

Evaluation of **1** and **2** for the treatment of NIDDM was problematic because of side effects. Although we hypothesized that the side effects may be due to RAR activities of the metabolites, represented by **18**−**21** for Targretin (Chart 3), this does not appear to be the case, since the metabolites were found to have minimal RAR activity.[28] In an effort to eliminate this problem a second generation of dihydronaphthalene analogues **3**−**5** were prepared for evaluation.

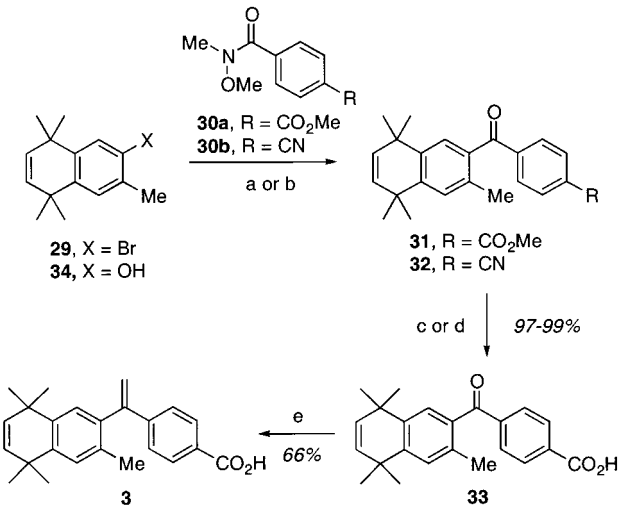
Synthesis of the Dihydronaphthalene Derivatives 3−5. The most direct approach to prepare **3**−**5** would involve Friedel−Crafts acylation of **22** with chloromethylterephthalate **14** using a procedure similar to that employed for the synthesis of **1**, followed by incorporation of the dihydronaphthalene unit after coupling via dehydration (Scheme 3). It has been reported that conversion of a keto-tetrahydronaphthalene to a dihydronaphthalene can successfully be performed using $POCl_3$/pyridine.[29] Thus, reaction of keto-tetrahydronaphthalene **22**, prepared in four steps and 50% overall yield from *p*-tolylacetic acid,[30] with **14** using $AlCl_3$ (4.0 equiv) afforded **23** in 62% yield. Olefination of **23** with methyltriphenylphosphonium ylide afforded olefin **24** in 57% yield. Reduction of **24** with $NaBH_4$ in MeOH gave alcohol **25** in 79% yield. Dehydration of **25** with $POCl_3$ in pyridine at 100 °C gave a quantitative yield of olefin **26**. Although **26** appeared to be a single compound by TLC and ^1H NMR, HPLC analysis indicated that it was a 4:1 mixture of compounds, and all attempts to purify **26** or its corresponding acid **3** proved unsuccessful.[31] It is assumed that the acidic conditions used in the elimination afforded a regioisomeric mixture of compounds, since this class of compounds are known to undergo methyl shift and ring contraction rearrangements.[32,33] The lack of success in the synthesis of **3** by the Friedel−Crafts chemistry led us to pursue a strategy in which the dihydronaphthylene unit was prepared prior to incorporation of the aryl ketone moiety.

Scheme 4[a]



[a] (a) $AlCl_3$, Br_2, CH_2Cl_2; (b) $TosNHNH_2$, *p*-TsOH, THF; (c) MeLi·LiBr complex, Et_2O.

Scheme 5[a]



[a] (a) 1.6 M *n*-BuLi in hexanes, THF; (b) Mg, 1,2-dibromoethane, THF; (c) KOH, $MeO(CH_2)_2OH$, water, reflux 16 h; (d) 50% aq NaOH, MeOH; (3) MeMgCl, THF; *p*-TsOH, toluene, reflux.

The bromo-dihydronaphthylene **29** was identified as the key intermediate for preparation of **3**−**5**, since it

(27) The minor *trans*-oxime **17** was obtained in high purity by successive recrystallization of the reaction mixture from MeOH.

(28) Neel, D.; Grese, T.; Wells, K.; Howell, S.; Shirley, M.; Ulm, E. In *220th National ACS Meeting*; American Chemical Society: Washington, DC, 2000; Vol. MEDI-068.

(29) Zhang, L.; Badea, B.; Enyeart, D.; Berger, E.; Mais, D.; Boehm, M. *J. Labeled Compd. Radiopharm.* **1995**, *36*, 701−712.

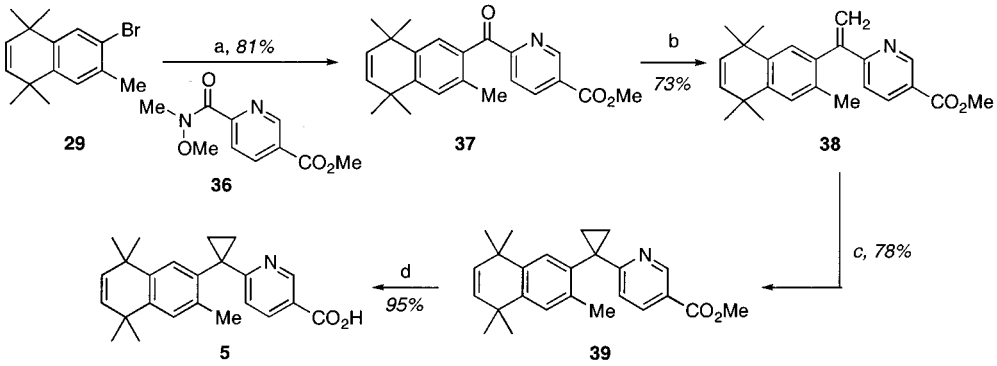
(30) Barclay, L.; Adams, K.; Foote, H.; Sanford, E.; Young, R. *Can. J. Chem* **1970**, *48*, 2763−2775.

(31) Purification of **4** by preparative HPLC was impractical as a result of solubility limitations of both compounds in the HPLC eluent.

(32) Naab, P.; Staab, H. *Chem. Ber* **1978**, *111*, 2982−2996.

(33) Staab, H.; Wittig, C.; Naab, P. *Chem. Ber.* **1978**, *111*, 2965−2981.

Scheme 6[a]



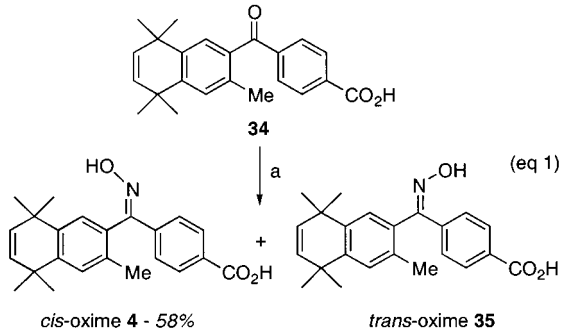
[a] (a) Mg, 1,2-dibromoethane, THF; (b) MeMgCl, THF; *p*-TsOH, toluene; (c) $(Me)_3SOI$, *tert*-KOBu, DMSO, THF; (d) NaOH, MeOH, then HCl.

would allow incorporation of the appropriate aryl ketone by either conversion into the corresponding organolithium or Grignard reagent and reaction with a suitable electrophile or by application of a Suzuki cross coupling reaction. Since acidic conditions had proved unsuccessful for incorporation of the olefin,[34] we decided to examine a synthesis of **29** from **22** using the Shapiro reaction (Scheme 4).[35] In addition, because of potential problems with bromination after the olfein was introduced, it was decided to incorporate the bromide into **22** prior to elimination. Thus, reaction of **22** with Br_2 and $AlCl_3$ (3.0 equiv) in CH_2Cl_2 afforded keto-bromide **27** in 86% yield. Treatment of **27** with *p*-toluenesulfonylhydrazide and catalytic *p*-TsOH in THF afforded tosylhydrazone **28** in 77% yield. Shapiro reaction of **28** with MeLi in Et_2O or methyl *tert*-butyl ether afforded a 99% yield of **29** with no rearrangement products or halogen metal exchange.[36] This completed an efficient seven-step synthesis of bromide **29** from *p*-tolyl acetic acid in 43% overall yield.

Conversion of **29** into the corresponding organolithium or Grignard reagent was achieved using either *n*-BuLi/−78 °C or Mg/1,2-dibromoethane, respectively (Scheme 5). Although reaction of the organolithium reagent with acid chloride **9** afforded multiple products, by using Weinreb amide **30a** a 16% yield of **31** was obtained in addition to 19% over addition products, due to competitive reaction at the ester functionality. However, when Weinreb amide **30b** was employed, nitrile **32** was prepared in 81% yield. Reaction of the Grignard reagent of **29** with **9** afforded a 53% yield of **31**, while using the Weinreb amide **30b** the yield was 51%. In addition to the lower yield the Grignard reactions were problematic because of competing formation of phenol **34**, which was extremely difficult to remove, even when THF, freshly distilled over Na, was utilized.

Saponification of **31** or hydrolysis of **32** afforded **33** in 97% and 99% yield, respectively. Subsequent treatment of **33** with MeMgCl followed by dehydration using *p*-TsOH (0.1 equiv) completed a 10-step synthesis of **3** in 23% overall yield.

cis-Oxime **4** was prepared by treatment of acid **34** with 50% aqueous NH_2OH in refluxing AcOH for 1 h (eq 1; (a) 50% NH_2OH, HOAc, reflux). A 9:1 mixture of *cis*- and



trans-oximes **4** and **35** were obtained, in addition to 3−6% of saturated analogue **2**. Recrystallization of the reaction mixture from 3:1 hexanes/EtOAc afforded **2** in 58% yield.[37] This completed a synthesis of **4** in nine steps and 20% yield.

The pyridyl analogue **5** was prepared using conditions similar to those used for **3** (Scheme 6). Coupling of Weinreb amide **36** with 2.0 equiv of the Grignard reagent derived from **29** afforded **37** in 81% yield. Reaction of **37** with MeMgCl, followed by dehydration with *p*-TsOH (0.5 equiv) afforded **38** in 73% yield. Cyclopropanation of **38** using trimethylsulfoxonium iodide/*tert*-KOBu in DMSO/THF afforded **39** in 78% yield. Saponification of **39** completed an 11-step synthesis of **5** in 18% overall yield.

Our final strategy to prepare this class of compounds was based upon the Suzuki cross coupling reaction.[38] Qing has examined coupling of the boronic acid derived from **40** in the synthesis of novel retinoid analogues.[39−44] By using chemistry that we developed for the synthesis of **29**, bromide **40** was prepared in 85% yield from **7** by

(34) Attempted elimination of a variety of leaving groups (MsO, TsO) from the alcohol of **22** proved was unsuccessful in formation of the dihydronaphthylene.

(35) Shapiro, R.; Heath, M. *J. Am. Chem. Soc.* **1967**, *89*, 5734−5735.

(36) Shapiro reaction of the tosylhydrazone generated from ketone **23** was also examined but was unsuccessful as a result of the competing reaction at the ketone and ester functionality under the basic conditions required for the elimination.

(37) Attempts to remove the **2** by further recrystallization from toluene or 9:1 ACN/IPA failed. Compound **2** was isolated by HPLC purification. This somewhat surprising result indicates that hydrogen was generated under the reaction conditions, and the effect of adding cyclohexene or some other simple additive to remove the hydrogen should be examined in future reactions.

(38) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(39) Qing, F.-L.; Yue, X.-J. *Chin. J. Chem* **2000**, *18*, 76−84.

(40) Qing, F.-L.; Yue, X.-J. *Tetrahedron Lett.* **1997**, *38*, 8067−8070.

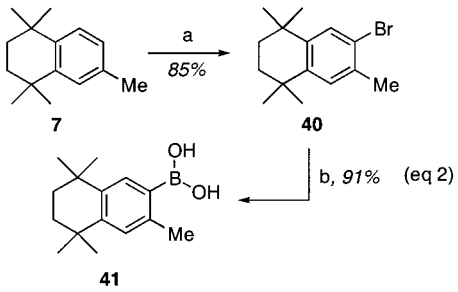
(41) Qing, F.-L.; Fan, J.; Sun, H.-B.; Yue, X.-J. *J. Chem. Soc., Perkin Trans. 1* **1997**, *20*, 3053−3057.

(42) Qing, F.-L.; Fan, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2117−2120.

(43) Yue, X.; Qing, F.-L.; Sun, H.-B.; Fan, J. *Tetrahedron Lett.* **1996**, *37*, 8213−8216.

(44) Wu, Q.; Dawson, M.; Zheng, Y.; Hobbs, P.; Agadir, A.; Jong, L.; Li, Y.; Liu, R.; Lin, B.; Zhang, X.-K. *Mol. Cell. Biol.* **1997**, *17*, 6598−6608.

treatment with $Br_2/AlCl_3$ (eq 2; (a) $AlCl_3$, Br_2, CH_2Cl_2; (b) (i) *n*-BuLi, THF; (ii) B(O-*i*-Pr)$_3$ at −78 °C, THF).



Bromides **40** and **29** were converted into the corresponding boronic acids **41** and **42** by treatment with *n*-BuLi and B(O-*i*-Pr)$_3$ at −78 °C in 91% and 81% yield, respectively. Vinyl triflate **43** was synthesized in 89% yield by treatment of methyl 4-acetylbenzoate with excess triflic anhydride and anhydrous Na_2CO_3 in CH_2Cl_2.[45]

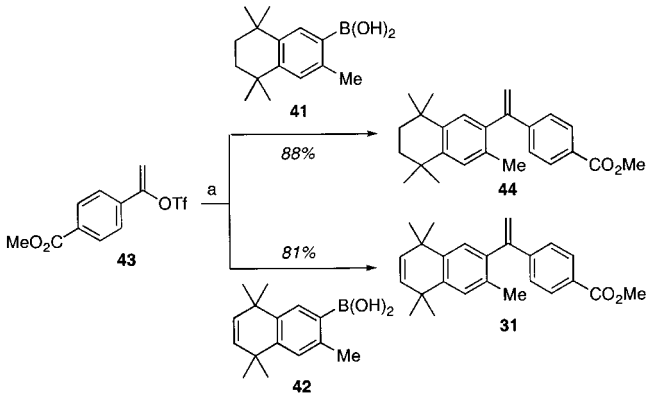
Initial examination of the conditions reported by Qing to effect Suzuki coupling of vinyl triflate **43** and boronic acid **41** using Pd(PPh$_3$)$_4$ in dioxane with either anhydrous bases or aqueous Na_2CO_3 afforded <35% yield of **44**, in addition to substantial decomposition. The yield of **44** increased to 56% when 3.0 equiv of vinyl triflate **43** was employed.

A variety of other catalysts [Pd(OAc)$_2$/PPh$_3$, Pd(dba)$_2$, (Ph$_3$P)$_2$PdCl$_2$] were examined but also afforded **44** in <30% yield. The optimal conditions identified for the Suzuki reaction were found to employ Pd(OAc)$_2$/P(*o*-Tol)$_3$ with Et$_3$N at 50 °C in DMF, which provided **44** in 88% yield (Scheme 7). This strategy completed a five-step synthesis of Targretin in 63% overall yield and is competitive with the reported process.[7] Using similar conditions **31** was prepared in 83% yield from **43** and **42**. This completed a 10-step synthesis of **3** in 22% overall yield and afforded a synthesis that was competitive with the organometallic approach.

Conclusion

Efficient synthesis of RXR agonists **1**−**5** have been developed. This chemistry employs two novel catalytic Friedel−Crafts reactions for the synthesis of **1** and **2**. A nitromethane-mediated Friedel−Crafts acylation of **7** was critical for successful synthesis of **1**. The presence of the pyridyl nitrogen allowed a selective chelate-controlled addition of MeMgCl to ketone **10** followed by elimination to generate olefin **11**. Cyclopropanation of ketone **10** with trimethylsulfoxonium ylide followed by saponification completed the synthesis of **1** in five steps and 33% yield. This synthesis has been employed to prepare kilogram quantities of **1** for clinical evaluation. *cis*-Oxime **2** was prepared in three steps and 34% yield using aqueous NH_2OH in AcOH. For the dihydronaphthylenes **3**−**5**, the key bromo-dihydronaphthalene derivative **29**, was prepared in seven steps and 47% yield, from *p*-tolylacetic acid, by application of the Shapiro reaction. Conversion of **29** into **3** and **4** was completed in three steps with 53% and 47% yield, respectively. The pyridyl analogue **5** was prepared from **29** in four steps and 43% yield. Suzuki coupling of boronic acids **41** and **42** with vinyl triflate **43** completed an efficient alternative synthesis of **3** and **44**, a penultimate intermediate in the synthesis of Targretin. These syntheses have been successfully employed to prepare multigram quantities of material for preclinical evaluation.

Scheme 7[a]



[a] (a) Pd(OAc)$_2$, P(*o*-Tol)$_3$, DMF, Et$_3$N, 50 °C.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral, combustion analysis, and IR were performed by the Eli Lilly and Co. Physical Chemistry Department.

1,1,4,4-Tetramethyl-1,2,3,4-tetrahydronaphthylene (7). 2,5-Dimethyl-2,5-hexanediol (391 g, 2.67 mol) was combined with reagent grade concentrated HCl (6 L) and stirred at ambient temperature for 3 h. Water (4 L) and CH_2Cl_2 (4 L) were then added to dissolve the solids. The layers were separated and the aqueous layer back-extracted with additional CH_2Cl_2 (1 L). The combined organic layers were dried ($MgSO_4$) and filtered using CH_2Cl_2 (1 L) to rinse. Toluene (372 g, 430 mL, 4.04 mol) was added to the CH_2Cl_2 solution and $AlCl_3$ (17.5 g, 0.131 mol) was added in portions over 25 min at ambient temperature while scrubbing vigorous HCl off-gassing. The reaction, which was complete upon addition of $AlCl_3$, was quenched with deionized water (4 L) while keeping the reaction temperature <25 °C. Heptane (4 L) was added and the organic layer was removed. The aqueous layer was back-extracted with additional heptane (1 L). The combined organic layers were washed with water (4 L) and brine (2 L) and dried ($MgSO_4$) and the solvent was removed in vacuo to give 538 g (99%) of **7** as a colorless oil that crystallized upon cooling.

Pyridine 2,5-Dicarboxylic Acid 5-Methyl Ester (8). To a suspension of dimethyl 2,5-pyridinedicarboxylate (1.26 kg, 6.45 mol) in MeOH (11.3 L) was added NaOH pellets (274 g, 6.85 mol) in one portion, and the mixture was stirred and heated to reflux for 1−4 h. Aqueous 2.0 N HCl (4.75 L, 10.7 mol) was then added dropwise at 60−75 °C over 20−60 min and the resultant slurry was allowed to stir and cool gradually to 15−20 °C with an ice−water bath. The reaction was filtered, rinsed with 2:1 MeOH/water (1.5 L), and then water (2 L). The wet cake was dried in a vacuum oven at 50−60 °C to yield 803 g (69%) of **8** as an off-white solid.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]nicotinate (10). To a suspension of **7** (750 g, 4.14 mol) in CH_2Cl_2 (5.3 L) under N_2 was added a catalytic amount of DMF (9.4 mL, 0.110 mol) followed by oxalyl chloride (380 mL, 4.35 mol) dropwise at 15−30 °C over 10−60 min. The reaction mixture was stirred at 15−30 °C for 1−4 h.

(45) Garcia Martinez, A.; Herrera, A.; Martinez, R.; Teso, E.; Garcia, A.; Osio, J.; Pargada, L.; Unanue, R.; Subramanian, L.; Hanack, M. *J. Heterocycl. Chem.* **1988**, *25*, 1237−1241.

Nitromethane (115 mL, 2.12 mol) and **7** (922 g, 4.56 mol) were charged, and the resulting mixture was stirred and cooled to 5−15 °C using an ice−water bath. $AlCl_3$ (1658 g, 12.4 mol) was added in portions at 5−30 °C over 10−30 min. The dark reaction mixture was allowed to stir at 15−30 °C for 12−24 h. The reaction mixture was added dropwise over 45−90 min at 15−35 °C to a separate flask containing deionized water (7.4 L) stirring in an ice−water bath. The quenched reaction mixture was stirred at 15−35 °C for 10−30 min and then the layers were separated. The upper aqueous layer was extracted with CH_2Cl_2 (1.4 L) and the combined organic layers were dried ($MgSO_4$). The reaction was filtered and rinsed with CH_2Cl_2 (1.5 L). The filtrate was concentrated in vacuo to a solid residue (1.54 kg). MeOH (6.2 L) was added, and the mixture was heated until all solids went into solution. The solution was allowed to stir and gradually cool to ambient temperature over 12−24 h to crystallize the product. After stirring in an ice−water bath at 0−10 °C for 1−2 h, the product was isolated by vacuum filtration and rinsed with cold MeOH (3.0 L). The wet cake was dried in a vacuum oven at 50−60 °C to yield 1033 g (68%) of **10** as an off-white solid.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethenyl]nicotinate (11). To a solution of **10** (3.40 kg, 9.3 mol) in toluene (34 L) at −10 to −5 °C under N_2 was added a 3.0 M solution of MeMgCl in THF (3.95 kg) over 15−120 min. Toluene (5.7 L) was used to rinse the MeMgCl solution. The reaction mixture was warmed to 20−25 °C, then quenched by addition to 1.0 N HCl (23 L) with stirring at 15−25 °C over 15−30 min. The reaction mixture was rinsed into the quench solution with more toluene (10 L). The layers were separated, and the organic layer was washed with deionized water (24 L). The combined aqueous layers were back extracted with toluene (10 L). The combined organic layers were filtered over $MgSO_4$ (5 kg) and rinsed with toluene (10 L). The filtrate was stirred at 20−25 °C as *p*-TsOH·H_2O (1.77 kg) was added. The solution was heated to reflux for 3−15 h to azeotrope water. The reaction solution was concentrated by atmospheric distillation to a total volume of ∼30 L. A solution of Na_2CO_3 (2.6 kg) in deionized water (48 L) was added to the concentrated reaction solution at 20−25 °C over 1−60 min, and the layers were separated. The lower aqueous layer was back extracted with toluene (10 L). The combined organic layers were concentrated by atmospheric distillation to a total volume of ∼14 L. MeOH (60 L) was added, and the mixture was again concentrated by atmospheric distillation to a total volume of ∼35 L. MeOH (15 L) was added, and the mixture was again concentrated by atmospheric distillation to a total volume of 14−20 L. The resulting slurry of product was stirred at 22−28 °C for 1−3 h, then filtered by nitrogen pressure, and rinsed with MeOH (10 L). After drying in a vacuum oven at 40−50 °C, 2.07 kg (61%) of **11** was obtained.

Methyl 6-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinate (12). To a stirred suspension of trimethylsulfoxonium iodide (726 g, 3.30 mol) in dry DMSO (2.4 L) was added potassium *tert*-butoxide, 20 wt % in THF (1876 g, 3.34 mol). A solution of **11** (800 g, 2.20 mol) in dry THF (9.6 L) was prepared separately and then added to the above suspension over 20−60 min at 20−30 °C. The reaction was stirred at 20−30 °C for 30−60 min and then quenched by addition of aqueous 2.0 N HCl (1.7 L, 3.5 mol HCl, 1.54 equiv) over 5−30 min. The two phase mixture was stirred at 20−35 °C for 15−60 min and deionized water (1.5 L) was added. The aqueous layer was back-extracted with EtOAc (2.0 L) and the combined organic layers were concentrated in vacuo to a solid residue (1491 g). MeOH (6.2 L) was added, and the resulting slurry was stirred at 40−50 °C for 30−60 min, then cooled to 15−25 °C. After stirring at 15−25 °C for 1−2 h, the product was isolated by vacuum filtration and rinsed with MeOH (3 L). The wet cake was dried in a vacuum oven at 50−60 °C to yield 681 g (82%) of **12** as a white to off-white solid.

6-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclopropyl]nicotinic Acid (1). To a stirred suspension of **12** (1.09 kg, 2.89 mol) in MeOH (10.9 L) was added aqueous 50% sodium hydroxide (460 mL, 8.79 mol), and the slurry was heated to 60−70 °C for 0.5−2 h until all solids went into solution and the reaction was complete. The hot solution was filtered and the filtrate solution was treated with aqueous 6.0 N HCl (1.5 L, 9.00 mol), added over 45−90 min at 50−70 °C, to precipitate the product. Deionized water (3.5 L) was added in one portion to dissolve the sodium chloride and the resultant slurry was stirred at 50−70 °C for 20−60 min and then cooled to 20−25 °C using an ice−water bath. After stirring at 20−25 °C for 0.5−2 h, the product was isolated by vacuum filtration, rinsed with 1:1 MeOH/water (1.2 L) and deionized water (3 L). The wet cake was dried in a vacuum oven at 50−60 °C to yield 1.04 kg (99%) of **1** as a white to off-white solid.

Methyl 4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate (15). To a solution of **7** (20.0 g, 98.8 mmol) and **14** (20.7 g, 98.8 mmol) in dichloroethane (20 mL) was added $FeCl_3$ (0.80 g, 4.93 mmol) and the reaction was heated to 75 °C for 16 h. The reaction was cooled and MeOH (60 mL) was added. The resultant light green slurry was stirred overnight at ambient temperature, then filtered, and rinsed with cold MeOH (60 mL) to give 29.3 g (81%) of **15**.

4-[(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic Acid (16). A suspension of **15** (29.3 g, 80.3 mmol) in MeOH (290 mL) was treated with 50 wt % NaOH (19.3 g, 12.7 mL, 0.24 mol) and the reaction was heated to reflux for 1−2 h. The reaction was then cooled to 55 °C and concentrated HCl (20.1 mL, 0.24 mol) added dropwise at <60 °C. The resultant slurry was cooled in an ice bath for 1 h and filtered to give 30.1 g (100%) of **16**.

4-[Hydroxyimino-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)]benzoic Acid (2). To a suspension of **12** (5.00 g, 14.3 mmol) in HOAc (100 mL) was added 50% aqueous NH_2OH (28.3 g, 26.2 mL, 0.43 mol). The reaction was heated to a gentle reflux for ∼1 h. Upon cooling in an ice bath the *cis*- and *trans*-oximes crystallized and were filtered, washed with water (40 mL), and dried to give 5.16 g (99%) of **2**:**17** in a ratio of 94:6 (HPLC). A portion of this material (5.00 g) was recrystallized from 3:1 hexanes/EtOAc (225 mL) to give 1.98 g of **2** (40% recovery and overall yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.92 (s, 1H), 11.47 (s, 1H), 7.86 (d, 2H, J = 8.35 Hz), 7.41 (d, 2H, J = 8.36 Hz), 7.19 (s, 1H), 6.87 (s, 1H), 1.59 (s, 4H), 1.95 (s, 2H), 1.18 (s, 6H), 1.11 (s, 6H); ^{13}C (75 MHz, DMSO-d_6) δ 166.94, 154.89, 144.23, 141.66, 140.43, 132.36, 130.90, 130.77, 129.45, 127.44, 126.14, 125.59, 34.63, 34.58, 33.68, 33.49, 31.56, 18.59; IR ($CHCl_3$) ν 2961, 2928, 2862, 1693 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.77; H, 7.40; N, 3.87 (PX 035379). A portion of the filtrate was purified to provide the *trans*-oxime **17**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.96 (s, 1H), 11.47 (s, 1H), 7.90 (d, 2H, J = 8.25 Hz), 7.46 (d, 2H, J = 8.24 Hz), 7.09 (s, 2H), 1.95 (s, 3H), 1.57 (s, 4H), 1.23 (s, 6H), 1.19 (s, 6H); ^{13}C (75 MHz, DMSO-d_6) δ 166.87, 154.61, 144.65, 141.58, 138.09, 133.95, 133.01, 130.50, 129.32, 128.87, 128.28, 127.74, 34.54, 34.48, 33.60, 33.40, 31.52, 31.43, 19.74; IR ($CHCl_3$) ν 2926, 2863, 1692, 1288 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.85; H, 7.47; N, 3.69.

1,1,4,4,6-Pentamethyl-1,3,4-trihydronaphthalene-2-one (22). A solution of 2-methyl-2-(*p*-tolyl)propanoic acid (10.0 g, 56.1 mmol) in CH_2Cl_2 and DMF (0.15 mL) was treated dropwise with oxalyl chloride (7.48 g, 5.14 mL, 58.9 mmol) and stirred at room temperature under N_2 for 2 h. The reaction was then cooled to −30 °C and catalytic $SnCl_4$ (2.23 g, 1.00 mL, 8.55 mmol) was added. After stirring at <−30 °C for 15 min, isobutylene (12.6 g, 0.224 mol) was condensed into the reaction at −78 °C via cannula. The reaction was allowed to warm to room temperature over 1.5 h and then heated to reflux for 2.5 h. The reaction was cooled and quenched with water (50 mL), and then the organic layer was washed with aqueous 1 N NaOH (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give 13.6 g of **22** as an oil that was crystallized from MeOH (30 mL) to afford 7.36 g (61%) of **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 1H, J = 8.05 Hz), 7.21 (s, 1H), 7.11 (d, 1H, J = 8.19 Hz), 2.69 (s, 2H), 2.39 (s, 3H), 1.52 (s, 6H), 1.34 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) 214.8, 143.9,

140.7, 136.4, 128.2, 127.6, 125.4, 52.0, 48.1, 38.3, 31.0, 28.9, 21.5; IR (KBr) ν 2965, 2928, 2870, 1711, 1499, 1462, 1380, 1366, 1313, 1237, 822 cm^{-1}; HRMS (FAB^+) *m/z* exact mass calcd for $C_{15}H_{21}O$ 217.1592, found 217.1589.

Methyl 4-[(3,5,5,8,8-Pentamethyl-7-oxo-2−5,6,8-trihydronaphthyl)carbonyl]benzoate (23). A solution of **22** (4.01 g, 18.5 mmol) and **14** (3.68 g, 18.5 mmol) in CH_2Cl_2 (60 mL) at 0 °C was treated with $AlCl_3$ (9.89 g, 74.2 mmol) in five portions over 20 min under N_2. The reaction mixture was heated to 45 °C, then the heating removed and the reaction was allowed to cool and stir at room temperature for 4 h. The reaction was cooled in an ice bath, quenched with water (200 mL), and extracted into EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 7.20 g of crude product that was triturated in hot MeOH (35 mL) and filtered to give 4.37 g of **23** (62%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, 2H, J = 8.38 Hz), 7.88 (d, 2H, J = 8.27 Hz), 7.32 (s, 1H), 7.30 (s, 1H), 3.97 (s, 3H), 2.69 (s, 2H), 2.39 (s, 3H), 1.41 (s, 6H), 1.39 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 213.9, 197.8, 166.7, 166.7, 147.0, 141.8, 140.8, 136.8, 136.1, 134.3, 134.2, 130.4, 130.1, 130.0, 129.0, 128.0, 52.9, 52.8, 51.6, 48.1, 38.5, 28.8, 20.5; IR (KBr) ν 1717, 1662, 1281, 1234 cm^{-1}; HRMS (FAB^+) *m/z* exact mass calcd for $C_{24}H_{27}O_4$ 379.1909, found 379.1912.

Methyl 4-[1-(3,5,5,8,8-Pentamethyl-7-oxo-2,5,6,8-trihydronaphthyl)vinyl]benzoate (24). Methyl triphenylphosphonium bromide (9.79 g, 27.4 mmol) was suspended in dry THF (60 mL), cooled to −30 °C under N_2, and treated with a 0.5 M solution of potassium bis(trimethylsilyl) amide in toluene (57 mL, 29 mmol) and warmed to 0 °C. The ylide solution was recooled to −30 °C and treated with a solution of **23** (4.15 g, 10.9 mmol) in dry THF (50 mL). The reaction was warmed to 0 °C for 45 min, quenched with water (150 mL), and extracted into Et_2O. The organic layer was dried ($MgSO_4$), and the solvent removed in vacuo to give 11.0 g of crude product that was column purified using 6:1 hexanes/EtOAc to give 2.36 g (57%) of **23**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, 2H, J = 8.43 Hz), 7.36 (d, 2H, J = 8.27 Hz), 7.19 (s, 1H), 7.17 (s, 1H), 5.89 (s, 1H), 5.36 (s, 1H), 3.93 (s, 3H), 2.69 (s, 2H), 2.05 (s, 3H), 1.47 (s, 6H), 1.37 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 214.4, 167.1, 149.1, 145.5, 143.5, 141.2, 140.0, 134.5, 130.1, 129.9, 129.7, 129.1, 126.9, 126.6, 117.4, 52.3, 52.0, 48.1, 38.2, 31.0, 28.9, 20.2; IR ($CHCl_3$) ν 3021, 2962, 1713, 1607, 1437, 1281 cm^{-1}; HRMS (FAB^+) *m/z* exact mass calcd for $C_{25}H_{28}O_3$ 376.2039, found 376.2042.

Methyl 4-[1-(7-Hydroxy-3,5,5,8,8-pentamethyl-2−5,6,7,8-tetrahydronaphthyl)vinyl]benzoate (25). A slurry of **24** (2.35 g, 6.24 mmol) in MeOH (80 mL) was treated with $NaBH_4$ (0.71 g, 18.8 mmol) in three portions at room temperature. The reaction mixture was heated until all of the solids dissolved, then cooled to room temperature and stirred for 1 h before being quenched with 1.0 N HCl (150 mL). The mixture was extracted into EtOAc, the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give crude product that was column purified using a gradient of 4:1 to 3:1 hexanes/EtOAc to give 1.87 g (79%) of **25**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 8.45 Hz), 7.36 (d, 2H, J = 8.41 Hz), 7.18 (s, 1H), 7.09 (s, 1H), 5.85 (s, 1H), 5.34 (s, 1H), 3.93 (s, 3H), 1.99 (s, 3H), 1.93 (t, 1H, J = 12.52 Hz), 1.78 (dd, 1H, J = 3.46 Hz, J = 12.80 Hz), 1.62 (bs, 1H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.21 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 167.3, 149.5, 145.8, 143.5, 141.8, 139.2, 133.7, 130.0, 129.6, 128.5, 128.4, 126.9, 117.9, 117.1, 73.1, 52.3, 43.6, 40.1, 35.5, 33.6, 32.8, 27.7, 24.8, 20.2; IR ($CHCl_3$) ν 3605, 3003, 2965, 2926, 2866, 1715, 1607, 1437, 1282 cm^{-1}; HRMS (FAB^+) *m/z* exact mass calcd for $C_{25}H_{30}O_3$ 378.2196, found 378.2199.

7-Bromo-1,1,4,4,6-pentamethyl-1,3,4-trihydronaphthalen-2-one (27). A solution of **22** (2.90 g, 13.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C was treated with powdered $AlCl_3$ (3.58 g, 26.8 mmol) and stirred at 0 °C for 5 min. Bromine (2.25 g, 14.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction was stirred at 0 °C for 30 min. The reaction was poured onto ice and extracted with EtOAc. The solvent was removed in vacuo to give 4.31 g of an oil that was crystallized from MeOH (8 mL) to give 3.40 g (86%) of **27**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.24 (s, 1H), 2.63 (s, 2H), 2.42 (s, 3H), 1.45 (s, 6H), 1.31 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 213.6, 143.3, 136.4, 131.4, 127.3, 123.7, 51.7, 48.1, 38.0, 30.9, 28.9, 22.9; IR (KBr) ν 2973, 1714, 1482, 1237, 1081 cm^{-1}; HRMS (FAB^+) *m/z* exact mass calcd for $C_{15}H_{20}OBr$ 295.0696, found 295.0698.

[Aza(7-bromo-1,1,4,4,6-pentamethyl(2−1,3,4-trihydronaphthylidene))methyl][(4-methylphenyl)-sulfonyl]-amine (28). A suspension of **27** (30.5 g, 0.10 mol), *p*-toluenesulfonylhydrazide (22.1 g, 0.119 mol), and *p*-toluenesulfonic acid monohydrate (4.92 g, 25.9 mmol) in MeOH (611 mL) was heated at reflux under N_2 for 24 h. The resultant reaction slurry was cooled for 1 h in an ice bath, filtered, and rinsed with cold MeOH (150 mL) to give 36.8 g (77%) of **28**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, 2H, J = 8.17 Hz), 7.77 (bs, 1H), 7.45 (s, 1H), 7.30 (d, 2H, J = 8.06 Hz), 2.45 (s, 2H), 2.42, (s, 3H), 2.36 (s, 3H), 1.41 (s, 6H), 1.15 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 164.2, 144.4, 143.5, 143.1, 136.0, 135.7, 131.1, 129.7, 128.6, 127.4, 123.5, 43.3, 37.4, 36.8, 30.5, 30.3, 22.8, 21.9; IR (KBr) ν 3222, 2973, 1597, 1482, 1470, 1388, 1378, 1366, 1346, 1185, 1169, 1075, 1011, 815, 707, 675, 566 cm^{-1}; MS (EI^+) calcd for $C_{22}H_{27}N_2O_2BrS$ 463, found *m/z* 463 (100%). Anal. Calcd for $C_{22}H_{27}N_2O_2BrS$: C, 57.02; H, 5.87; N, 6.04; Br, 17.24. Found: C, 57.08; H, 6.04; N, 6.08; Br, 17.54.

6-Bromo-1,1,4,4,7-pentamethyl-1,4-dihydronaphthalene (29). A suspension of **28** (20.0 g, 43.2 mmol) in MTBE (400 mL) was treated with a 1.5 M solution of MeLi as a complex with LiBr in Et_2O (86.3 mL, 0.13 mol) at room temperature under N_2. The reaction was stirred at room temperature for 1 h, cooled to 0 °C, and quenched with water (500 mL). The reaction was extracted with MTBE (1 L), the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 12.0 g (99%) of **29** as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.23 (s, 1H), 5.52 (s, 2H), 2.41 (s, 3H), 1.35 (s, 12H); ^{13}C (125 MHz, $CDCl_3$) δ 142.8, 142.3, 135.4, 133.2, 133.1, 130.3, 129.0, 122.8, 35.5, 35.4, 32.9, 32.9, 22.9; IR (KBr) ν 3014, 2961, 2922, 2864, 1485, 1455, 1080, 889, 765 cm^{-1}; MS (FD) calcd for $C_{15}H_{19}Br$ 279, found *m/z* 279 (100%). Anal. Calcd for $C_{15}H_{19}Br$: C, 64.52; H, 6.86; Br, 28.62. Found: C, 64.99; H, 6.76; Br, 28.30.

Methyl 4-(*N*-methoxy-*N*-methylcarbamoyl)benzoate (30a). A solution of K_2CO_3 (19.1 g, 0.14 mol) in water (75 mL) was cooled to −5 °C and treated with *N*,*O*-dimethylhydroxyamine hydrochloride (6.14 g, 62.9 mmol) and MTBE (75 mL). To the reaction was added **9** (15.0 g, 75.5 mmol) in portions over 10 min and the resultant mixture was warmed to room temperature for 1 h. The reaction was diluted with water and extracted with EtOAc and the organic layer was dried ($MgSO_4$). The solvent was removed in vacuo to give 15.9 g of product that was purified by column chromatography using 1:1 hexanes/EtOAc to give 8.56 g (61%) of **30a**: ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, 2H, J = 8.24 Hz), 7.72 (d, 2H, J = 8.32 Hz), 3.94 (s, 3H), 3.53 (s, 3H), 3.37 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.4, 166.8, 138.8, 132.2, 129.6, 128.5, 61.6, 52.7, 33.8; IR (KBr) ν 1722, 1639, 1438, 1282, 1118, 1109 cm^{-1}; MS (EI^+) calcd for $C_{11}H_{13}NO_4$ 223, found *m/z* 224 (M + 1, 100%). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.15; H, 5.92; N, 6.29.

(4-Cyanophenyl)-*N*-methoxy-*N*-methylformamide (30b). 4-Cyanobenzoyl chloride (8.00 g, 48.3 mmol), *N*,*O*-dimethylhydroxyamine hydrochloride (7.07 g, 72.5 mmol), and K_2CO_3 (10.0 g, 72.5 mmol) were combined in a mixture of ACN (100 mL) and water (50 mL) and stirred for 16 h at room temperature. The reaction was diluted with water and extracted with EtOAc, the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 7.63 g (83%) of **30b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2H, J = 8.14 Hz), 7.70 (d, 2H, J = 8.40 Hz), 3.51 (s, 3H), 3.37 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 168.4, 138.8, 132.2, 129.2, 118.5, 114.6, 61.7, 33.6; IR (KBr) ν 3020, 2233, 1641, 1423, 1386, 982, 848 cm^{-1}; MS (EI^+) calcd for $C_{10}H_{10}N_2O_2$ 190, found *m/z* 191 (M + 1, 100%). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.01; H, 5.36; N, 14.98.

4-[(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)carbonyl]benzenecarbonitrile (32). A −78 °C solution of **29** (2.00 g, 7.16 mmol) in dry THF (25 mL) was treated dropwise with 1.6 M *n*-BuLi in hexanes (5.40 mL, 8.60 mmol) over 10 min and the reaction was stirred at −78 °C for 20 min under N_2. The reaction solution was transferred via cannula to a −78 °C solution of **30b** (1.23 g, 6.47 mmol) in dry THF (10 mL). The combined reaction mixture was stirred for 15 min at −78 °C and then warmed to room temperature before being quenched with 1.0 N HCl (75 mL). The reaction was extracted with EtOAc, the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.70 g of product that was purified by column chromatography using 9:1 hexanes/EtOAc to give 1.73 g (81%) of **32**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 2H, J = 8.27 Hz), 7.79 (d, 2H, J = 8.30 Hz), 7.32, (s, 1H), 7.31 (s, 1H), 5.56 (s, 2H), 2.40 (s, 3H), 1.41 (s, 6H), 1.30 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 197.0, 146.7, 142.2, 140.4, 135.4, 135.0, 133.1, 133.1, 132.6, 130.8, 129.7, 128.3, 118.4, 116.5, 35.8, 35.3, 33.1, 33.0, 32.9, 32.8, 20.4; IR (KBr) ν 3025, 2962, 2924, 2229, 1671, 1460, 1444, 1361, 1313, 1298, 1262, 1243, 1180, 885, 857, 778, 769 cm^{-1}; MS (EI$^+$) calcd for $C_{23}H_{23}NO$ 329, found m/z 330 (M + 1, 100%). Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 84.06; H, 7.23; N, 4.33.

4-[(3,5,5,8,8-pentamethyl-2−5,8-dihydronaphthyl)carbonyl]benzoic Acid (33). A suspension of **32** (1.62 g, 4.92 mmol) in 2-methoxyethanol (20 mL) was treated with 85% KOH (1.62 g, 24.5 mmol) in water (10 mL), and the mixture was heated to reflux for 16 h to give a yellow solution. The reaction was cooled, quenched with 1.0 N HCl (50 mL), and extracted with EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo using toluene to azeotropically remove residual 2-methoxyethanol to give 1.66 g (97%) of **33** as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.22 (bs, 1H), 8.09 (d, 2H, J = 8.24 Hz), 7.81 (d, 2H, J = 8.33 Hz), 7.42 (s, 1H), 7.36 (s, 1H), 5.56 (s, 2H), 2.27 (s, 3H), 1.36 (s, 6H), 1.25 (s, 6H); ^{13}C (125 MHz, DMSO-d_6) δ 197.9, 167.5, 146.0, 141.7, 140.3, 136.2, 135.4, 134.7, 133.5, 133.4, 130.5, 130.4, 129.7, 127.9, 35.8, 35.4, 32.9, 32.9, 20.3; IR (KBr) ν 2963, 2956, 2924, 1691, 1658, 1427, 1314, 1296, 1262, 1254, 767, 745 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{23}H_{25}O_3$ 349.1804, found 349.1800.

4-[1-(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)vinyl]benzoic Acid (3). A 3.0 M solution of MeMgCl in THF (1.53 mL, 4.60 mmol) was diluted with dry THF (3 mL) and cooled to −10 °C under N_2. A solution of **33** (0.40 g, 1.15 mmol) in THF (4 mL) was added dropwise at < −5 °C, and the reaction was stirred at 0−5 °C for 4 h until complete. The reaction was quenched with 1.0 N HCl (15 mL) and extracted with toluene and water and the solvent was removed in vacuo to give the intermediate tertiary alcohol as a white solid. This intermediate was combined with *p*-toluenesulfonic acid monohydrate (0.02 g, 0.116 mmol) and toluene (30 mL) and heated to reflux, allowing the distillate to condense in a Dean−Stark trap prefilled with toluene. The dehydration was complete after 2 h and the reaction cooled and was extracted with water and EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 0.37 g of crude product that was purified by column chromatography using 100% EtOAc to give 0.26 g (66%) of **3** as a solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.83 (s, 1H), 7.91 (d, 2H, J = 8.29 Hz), 7.37 (d, 2H, J = 8.30), 7.25 (s, 1H), 7.17 (s, 1H), 5.93 (s, 1H), 5.54 (s, 2H), 5.30 (s, 1H), 1.95 (s, 3H), 1.39 (s, 6H), 1.29 (s, 6H); ^{13}C (125 MHz, DMSO-d_6) δ 167.9, 149.0, 145.2, 142.4, 140.6, 139.1, 133.8, 133.4, 130.8, 130.5, 129.0, 128.4, 127.8, 127.1, 118.0, 35.5, 35.4, 33.2, 33.1, 20.4; IR (KBr) ν 3070, 3020, 2964, 2953, 2920, 2901, 2865, 2666, 2541, 1676, 1608, 1460, 1420, 1358, 1316, 1279, 1112, 909, 904, 866, 787, 760 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{24}H_{27}O_2$ 347.2011, found 347.2006.

4-[(Hydroxyimino)(3,5,5,8,8-pentmethyl(2−5,8-dihydronaphthyl))methyl]benzoic Acid (4). A suspension of **34** (2.00 g, 5.74 mmol) in glacial acetic acid (20 mL) was treated with 50% aqueous NH_2OH (7.0 mL, 0.11 mol) and the mixture was heated to a gentle reflux for 1.5 h to give a solution that was then cooled to room temperature. The reaction was diluted with water and extracted with EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 3.29 g of *trans*- and *cis*-oximes as a 1:9 ratio, as well as 6% of the reduced *cis*-oxime **2**. This material was recrystallized from 3:1 hexanes/EtOAc (70 mL) and placed in the freezer overnight. The slurry was filtered using 10 mL of cold 3:1 hexanes/EtOAc as a rinse to give 1.20 g of **4** (58%) as a white solid that contained no *trans*-oxime but still contained 8% of the reduced *cis*-oxime **2**. A portion of this material was purified by preparative HPLC to remove **2**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.49 (s, 1H), 7.93 (d, 2H, J = 8.31 Hz), 7.49 (d, 2H, J = 8.35 Hz), 7.35 (s, 1H), 7.04 (s, 1H), 5.54 (s, 2H), 2.06 (s, 3H), 1.36 (s, 6H), 1.26 (s, 6H); ^{13}C (125 MHz, DMSO-d_6) δ 167.8, 155.7, 142.9, 141.3, 140.5, 133.7, 132.2, 131.7, 130.4, 128.1, 127.0, 126.2, 117.8, 35.6, 35.5, 33.1, 33.1, 19.9; IR (KBr) ν 3015, 2961, 2924, 2867, 1694, 1285 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{24}H_{26}NO_3$ 364.1913, found 364.1915.

Methyl 6-(*N*-Methoxy-*N*-methylcarbamoyl)pyridine-3-carboxylate (36). A solution of **8** (22.8 g, 0.13 mol) in CH_2Cl_2 (250 mL) was treated with 2 drops of DMF followed by oxalyl chloride (15.9 g, 11.0 mL, 0.13 mmol). The reaction stirred at room temperature under N_2 for 1 h and then cooled to −5 °C and *N*,*O*-dimethylhydroxyamine hydrochloride (12.9 g, 0.13 mol) and pyridine (21.9 g, 22.0 mL, 0.28 mol) were added. The reaction was warmed to room temperature until complete and then quenched with aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic layer was washed with 1.0 N HCl and dried (Na_2SO_4). The solvent was removed in vacuo to give an oil from which residual pyridine was removed by azeotrope with heptane, and the crude product was recrystallized from hexanes/EtOAc to give 14.4 g of **36**. An additional 7.86 g of material was obtained by column purification of the filtrate using 1:4 hexanes/EtOAc to give a total of 22.3 g of **36** (79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.21 (d, 1H, J = 0.94 Hz), 8.38 (dd, 1H, J = 1.96 Hz, 8.16 Hz), 7.70 (bs, 1H), 3.98 (s, 3H), 3.74 (bs, 3H), 3.41 (bs, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 165.8, 157.4, 150.4, 138.4, 127.4, 123.1, 62.4, 53.3, 33.3; IR (KBr) ν 1720, 1656, 1591, 1276, 1115, 1019, 1002, 747 cm^{-1}; MS (EI$^+$) calcd for $C_{10}H_{12}N_2O_4$ 224, found m/z 225 (M + 1, 100%). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.38; H, 5.38; N, 12.54.

Methyl 6-[(3,5,5,8,8,-Pentamethyl-2−5,8-dihydronaphthyl)carbonyl]pyridine-3-carboxylate (37). A suspension of magnesium turnings (0.12 g, 4.85 mmol) in dry THF (0.5 mL) was treated with 3 drops of 1,2-dibromoethane under N_2 followed by a solution of **29** (0.90 g, 3.22 mmol) in dry THF (4 mL), allowing the reaction to exotherm during the addition. The Grignard solution was stirred at room temperature for 1 h and transferred via cannula to a −78 °C solution of **36** (0.36 g, 1.61 mmol) in dry THF (4 mL). The reaction mixture was stirred for 15 min at −78 °C, then warmed to room temperature and stirred for 1 h. The reaction was quenched with 1.0 N HCl (10 mL) and extracted with EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give the product, which was purified by column chromatography using 9:1 hexanes/EtOAc to give 0.47 g (81%) of **37** as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, 1H, J = 1.62 Hz), 8.51 (dd, 1H, J = 1.94 Hz, J = 8.07 Hz), 8.13 (d, 1H, J = 8.23 Hz), 7.53 (s, 1H), 7.30 (s, 1H), 5.54 (s, 2H), 4.02 (s, 3H), 2.44 (s, 3H), 1.39 (s, 6H), 1.31 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 196.2, 165.5, 159.0, 150.4, 147.0, 139.9, 138.5, 136.4, 134.3, 133.3, 133.1, 130.3, 129.7, 128.2, 124.1, 53.0, 35.8, 35.3, 32.8, 32.7, 20.9; IR (KBr) ν 2958, 2969, 2953, 1730, 1660, 1432, 1274, 1114, 1021, 750 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{23}H_{26}NO_3$ 364.1913, found 364.1908.

Methyl 6-[1-(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)vinyl]pyridine-3-carboxylate (38). A solution of **37** (1.22 g, 3.36 mmol) in dry THF (18 mL) was cooled to −25 °C under N_2 and treated dropwise with a 3.0 M solution of MeMgCl in THF (1.40 mL, 4.20 mmol) at < −20 °C. The reaction was warmed to room temperature and stirred for 2 h until complete. The reaction was quenched with 1 N HCl (75 mL), extracted with toluene, and dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.28 g of the tertiary

alcohol intermediate. This intermediate was combined with *p*-toluenesulfonic acid monohydrate (0.32 g, 1.68 mmol) in toluene (75 mL) and heated to reflux, allowing the distillate to condense in a Dean−Stark trap prefilled with toluene. The dehydration was complete after 11 h, and the reaction was cooled and extracted with aqueous 5% $NaHCO_3$ (75 mL) and EtOAc. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 1.18 g of crude product that was purified by column chromatography using 9:1 hexanes/EtOAc to give 0.89 g (73%) of **38** as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, 1H, J = 2.10 Hz), 8.18 (dd, 1H, J = 2.04 Hz, J = 8.26 Hz), 7.22 (d, 2H, J = 11.24 Hz), 7.06 (d, 1H, J = 8.26 Hz), 6.60 (d, 1H, J = 1.92 Hz), 5.57, (s, 1H), 5.56 (s, 2H), 3.97 (s, 3H), 2.06 (s, 3H), 1.40 (s, 6H), 1.36 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 166.2, 161.5, 151.1, 148.4, 142.7, 140.8, 138.1, 137.7, 133.6, 133.5, 133.4, 128.2, 128.1, 124.7, 121.5, 52.7, 35.5, 35.4, 33.1, 20.3; IR (KBr) ν 2966, 2952, 1722, 1592, 1437, 1285, 1270, 1115, 767 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{24}H_{28}NO_2$ 362.2123, found 362.2120.

Methyl 6-[(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)cyclopropyl]pyridine-3-carboxylate (39). A suspension of trimethylsulfoxonium iodide (0.80 g, 3.65 mmol) in dry DMSO (8 mL) was treated with a 1.0 M solution of *tert*-KOBu in THF (3.70 mL, 3.69 mmol) at room temperature under N_2, and the resultant ylide solution was stirred for 30 min. A solution of **38** (0.88 g, 2.43 mmol) in dry THF (16 mL) was added dropwise to the ylide solution at room temperature and the reaction was stirred for 1 h. The reaction was quenched with 1 N HCl (50 mL) and extracted with EtOAc, the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude product that was purified by column chromatography using 9:1 hexanes/EtOAc to give 0.71 g (78%) of **39** as a solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, 1H, J = 1.77 Hz), 8.01 (dd, 1H, J = 2.11 Hz, J = 8.36 Hz), 7.37 (s, 1H), 7.21 (s, 1H), 6.80 (d, 1H, 8.31 Hz), 5.56 (s, 2H), 3.97 (s, 3H), 2.18 (s, 3H), 1.88 (d, 2H, J = 3.04 Hz), 1.40 (s, 8H), 1.36 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 169.6, 166.5, 150.9, 142.0, 140.9, 138.1, 137.0, 136.6, 133.6, 133.5, 129.3, 128.4, 122.7, 121.1, 117.9, 52.5, 35.4, 35.4, 33.1, 33.1, 30.8, 20.6, 19.7; IR (KBr) ν 2965, 2953, 1716, 1595, 1440, 1289, 1272, 1117, 1138, 1022, 787, 765 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{25}H_{30}NO_2$ 376.2281, found 376.2277.

6-[(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)cyclopropyl]pyridine-3-carboxylic Acid (5). A suspension of **39** (0.70 g, 1.86 mmol) in MeOH (35 mL) was treated with 50% aqueous NaOH (0.75 g, 9.38 mmol) and heated to reflux for 1.5 h until the hydrolysis was complete. The hot reaction solution was acidified using 1 N HCl (11 mL) at which point the product crystallized. The slurry was cooled to room temperature, stirred for 2 h, and filtered using the filtrate as an initial rinse and then water (20 mL) as a final rise to give 0.639 g (95%) of **5** after drying the solid in a vacuum oven at 50 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.13 (bs, 1H), 8.98 (s, 1H), 8.04 (d, 1H, J = 7.40 Hz), 7.36 (s, 1H), 7.27 (s, 1H), 6.75 (d, 1H, J = 8.15 Hz), 5.53 (s, 2H), 2.20 (s, 3H), 1.74 (s, 2H), 1.32 (s, 8 H), 1.29 (s, 6H); ^{13}C (125 MHz, DMSO-d_6) δ 168.7, 167.1, 151.0, 141.8, 140.8, 138.4, 137.9, 136.6, 133.8, 133.8, 129.2, 128.7, 124.0, 121.0, 35.5, 33.2, 33.1, 31.0, 20.5, 19.8; IR (KBr) ν 3014, 2965, 2922, 2866, 1680, 1595, 1422, 1379, 1296, 1275 cm^{-1}; HRMS (FAB$^+$) m/z exact mass calcd for $C_{24}H_{28}NO_2$ 362.2120, found 362.2116. Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.98; H, 7.40; N, 3.75.

Methyl 4-{1-[(Trifluoromethyl)sulfonyloxy]vinyl}benzoate (43). To a solution of methyl 4-acetylbenzoate (4.00 g, 22.4 mmol) in 34 mL of CH_2Cl_2 at room temperature was added Na_2CO_3 (4.75 g, 44.8 mmol). Triflic anhydride (10.4 mL, 67.4 mmol) in 46 mL of CH_2Cl_2 was added dropwise, and the resulting suspension was stirred vigorously for 40 h. The reaction was filtered through Celite, and the filtrate was washed with 2 × 100 mL saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting yellow solid was purified by column chromatography using 20% EtOAc in hexane to provide 6.18 g (89%) of triflate **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H), 5.73 (d, J = 4.3 Hz, 1H), 5.50 (d, J = 4.3 Hz, 1H), 3.94 (s, 3 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.4, 151.3, 135.4, 132.0, 131.0, 130.0, 129.3, 125.3, 108.8, 52.3 ppm; IR ($CHCl_3$) 2900, 1723, 1423, 1285, 1141, 942 cm^{-1}; Anal. Calcd for $C_{11}H_9F_3O_5S$: C, 42.59; H, 2.92. Found: C, 42.58; H, 2.95.

5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl-boronic Acid (41). To a −78 °C solution of *n*-BuLi (9.84 mL, 1.30 M in hexane, 12.8 mmol) in 30 mL of THF was added a solution of bromide **40** (3.00 g, 10.7 mmol) in 8 mL of THF (5 mL THF rinse) via cannula over 20 min. The resulting solution was stirred for 10 min, and a solution of B(O-*i*-Pr)$_3$ (4.01 g, 21.3 mmol) in 10 mL of THF was added over 20 min. The reaction mixture was stirred at −78 °C for 1 h, warmed to room temperature for 2 h, and quenched with 35 mL of aqueous 3 M HCl. After 2 h at room temperature, the mixture was diluted with EtOAc (60 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude white solid was filtered through silica gel with 25% EtOAc in hexane to provide 2.38 g (91%) **41** that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.20 (s, 1H), 2.80 (s, 3H), 1.72 (s, 4H), 1.35 (s, 6H), 1.33 (s, 6H); IR ($CHCl_3$) ν 2963, 2928, 2862, 1604, 1392, 1380, 1342, 1333 cm^{-1}.

3,5,5,8,8-Pentamethyl-5,8-dihydronaphthalene-2-boronic Acid (42). To a −78 °C solution of *n*-BuLi (4.92 mL, 1.60 M in hexane, 7.88 mmol) in 20 mL of THF was added a solution of bromide **29** (2.00 g, 7.16 mmol) in 5 mL of THF (5 mL THF rinse) via cannula over 20 min. The resulting solution was stirred for 10 min, and a solution of B(O-*i*-Pr)$_3$ (2.69 g, 14.3 mmol) in 5 mL of THF was added over 20 min. The reaction mixture was stirred at −78 °C for 2 h and was warmed to room temperature for 1 h. The resulting suspension was quenched with 3 M HCl (30 mL). After 30 min at room temperature, the mixture was diluted with EtOAc (75 mL) and the phases were separated. The organic layer was washed with saturated aqueous NaCl (35 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude white solid was filtered through silica gel with 33% EtOAc in hexane to provide 1.42 g (81%) **42** that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.20 (s, 1H), 5.42 (m, 2H), 2.80 (s, 3H), 1.35 (s, 6H), 1.30 (s, 6H); IR ($CHCl_3$) ν 3008, 2962, 1606, 1462, 1392, 1367, 1360, 1289, 1113 cm^{-1}.

Methyl 4-[1-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]-benzoate (44). A solution of boronic acid **41** (0.10 g, 0.41 mmol), triflate **43** (0.18 g, 0.56 mmol), Pd(OAc)$_2$ (0.005 g, 0.024 mmol), P(*o*-Tol)$_3$ (14.6 g, 0.05 mmol), and Et_3N (0.17 mL, 1.22 mmol) in DMF (2 mL) was heated to 50 °C for 2 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (20 mL) and H_2O (15 mL). The organic layer was washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The brown solid was chromatographed using 5% EtOAc in hexane to provide 0.13 g (88%) **44**.

Methyl 4-[(3,5,5,8,8-Pentamethyl-2−5,8-dihydronaphthyl)carbonyl]benzoate (31). A solution of boronic acid **42** (0.10 g, 0.41 mmol), triflate **43** (0.18 mg, 0.57 mmol), Pd(OAc)$_2$ (0.005 g, 0.02 mmol), P(*o*-Tol)$_3$ (0.015 g, 0.05 mmol), and Et_3N (0.17 mL, 1.22 mmol) in DMF (2.0 mL) was heated to 50 °C for 2 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (20 mL) and H_2O (15 mL). The organic layer was washed with H_2O (10 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The brown solid was purified by column chromatography using 5% EtOAc in hexane to provide 0.12 g (83%) **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), δ 7.36 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 7.15 (s, 1H), 5.84 (s, 1H), 5.54 (s, 2H), 5.35 (s, 1H), 3.91 (s, 3H), 1.98 (s, 3H), 1.37 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.9, 147.9, 144.7, 141.5, 139.7, 138.1, 132.8, 132.5, 129.5, 129.0, 128.6, 127.6, 127.0 126.6, 117.7, 52.0, 34.6, 34.5, 32.2, 32.2, 19.5 ppm; IR ($CHCl_3$) 2961, 1716, 1607, 1437, 1283, 1111 cm^{-1}; exact mass calcd for $C_{25}H_{29}O_2$ 361.2167, found 361.2171.

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